

Developmental Physiologically-Based Pharmacokinetic Modeling of Perfluorooctane Sulfonate in Rats and Mice

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I. Introduction

Perfluorooctane sulfonate (PFOS) is a member of a class of perfluorinated compounds (PFCs) used in (Renner, 2001):

- ❖ coatings for paper products (e.g. paper plates, microwave popcorn bags),
- ❖ oil- and water-repellent products for fabrics and carpets,
- ❖ airplane hydraulic fluid,
- ❖ fire-fighting foams, and
- ❖ floor polishes.

Wildlife Exposure

PFOS has been detected in the liver and blood of wildlife in North America, Europe, Asia, and Antarctica (Kannan et al., 2001).

Human Exposure

- ❖ PFOS was detected in the serum of 3M fluorochemical production workers during voluntary medical surveillances in 1995 and 1997 (Olsen et al, 1999).
- ❖ PFOS was also found in liver and blood samples from non-occupationally exposed human donors (Olsen, 2003).

Toxicity of PFOS in Rats

The critical effects of PFOS exposure in rats include (Seacat et al., 2002)

- ❖ hepatocellular hypertrophy and vacuolation,
- ❖ decreased serum cholesterol and triglycerides,
- ❖ increased liver-to-body-weight ratios,
- ❖ decreased body weight, and
- ❖ death.

The **developmental effects** of maternal PFOS exposure in rats include reduced pup viability, growth, and survival (3M, 1999).

Environmental Concern

- ❖ The persistence and wide distribution of PFOS in the environment have caused a growing concern about its potential health risk on humans.

- ❖ In May 2000, 3M Corporation announced that they would stop manufacturing a group of perfluorinated compounds because of this concern. PFOS, one of the chemicals in the group, is a metabolite of the other chemicals.

- ❖ Therefore, exposure to PFOS could occur directly from its manufacture or indirectly from the degradation of other perfluorinated chemicals.

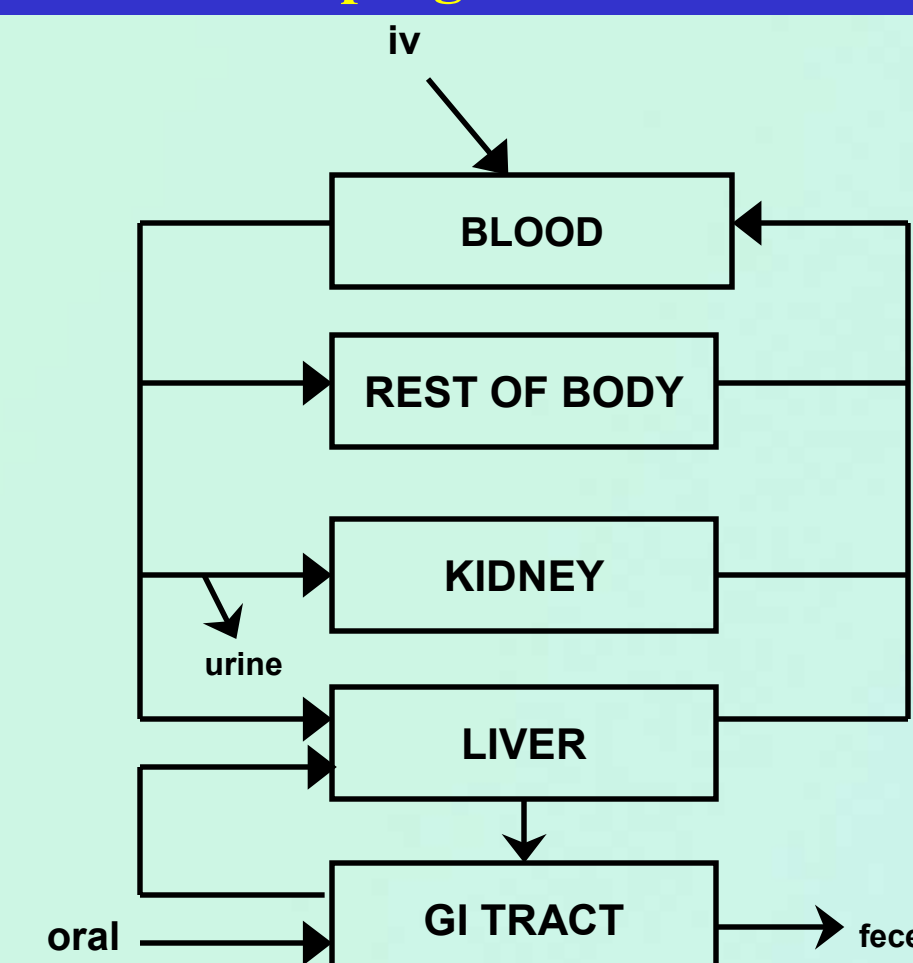
Objective

- ❖ The purpose of this project is to develop and utilize a developmental physiologically-based pharmacokinetic (PBPK) model that will describe PFOS kinetics in adult male and female, pregnant, lactating, fetal, and neonatal rats (and potentially mice) following oral and intravenous exposure.

- ❖ The model will be used to estimate internal doses for these different life stages to help in evaluating dose-response observations.

II. Methods

A. Initial Model: Nonpregnant Rats and Mice



Pharmacokinetics of PFOS in Rats

- ❖ Well absorbed after oral administration
- ❖ Distributes primarily to the liver and the blood
- ❖ Poorly eliminated from the body; elimination half-life > 89 days
- ❖ Appears to undergo enterohepatic recirculation
- ❖ No evidence of further metabolism

C. Parameters and Experimental Data

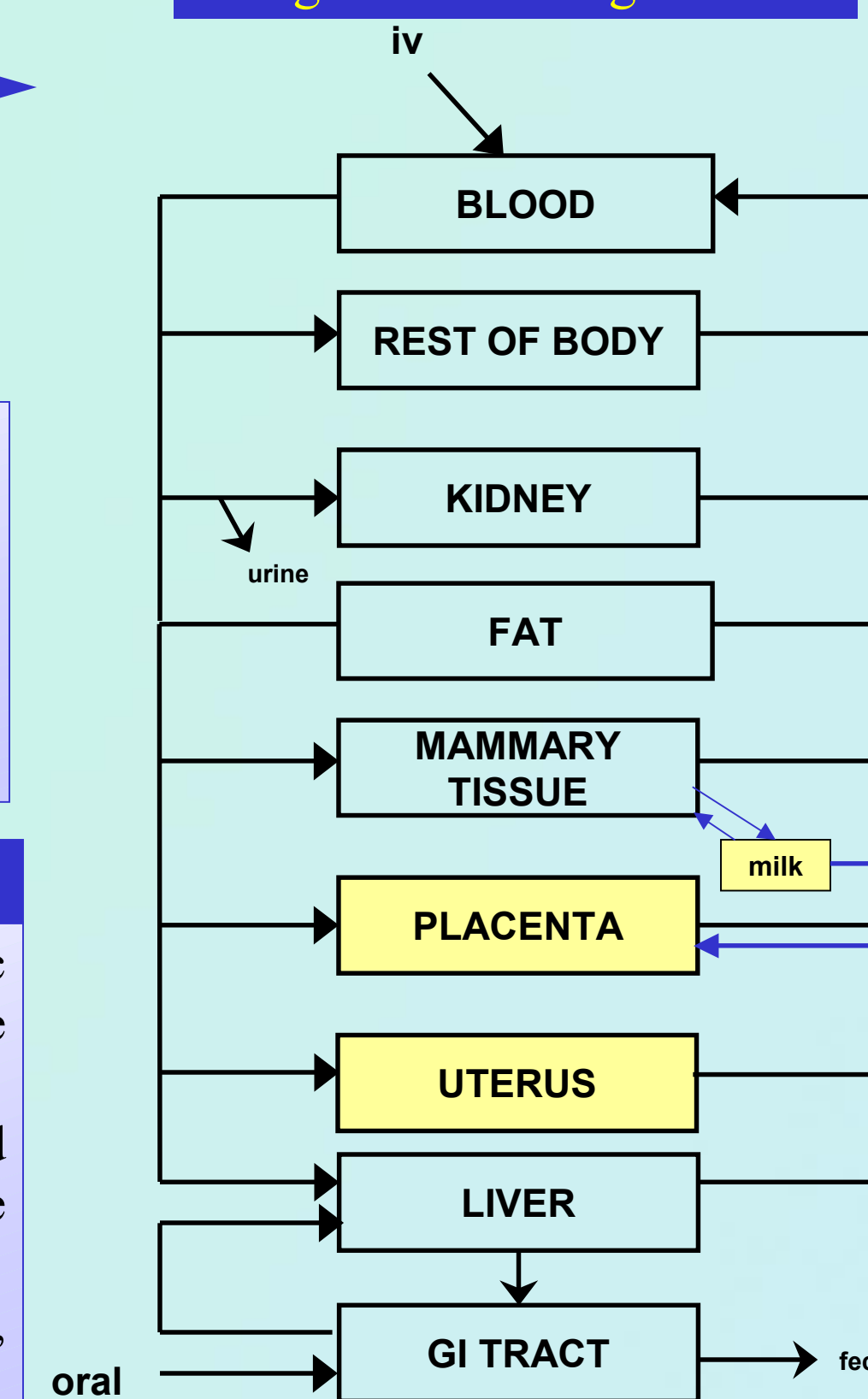
- Organ- and species-specific parameters such as blood flow, cardiac output, ventilation rates and organ volumes will be obtained from the literature.
- Chemical-specific parameters (e.g., partition coefficients and absorption rates) that are included in the model equations will be estimated using experimental data.
- Available data sets include blood and tissue levels following iv, oral, and chronic feeding exposures in adult, nonpregnant and pregnant rats.

B. Extended Model: Pregnant, Lactating, Fetal, and Neonatal Rats and Mice

The adult model will be extended to simulate PFOS kinetics in pregnant, lactating, fetal, and neonatal rats and mice by adding

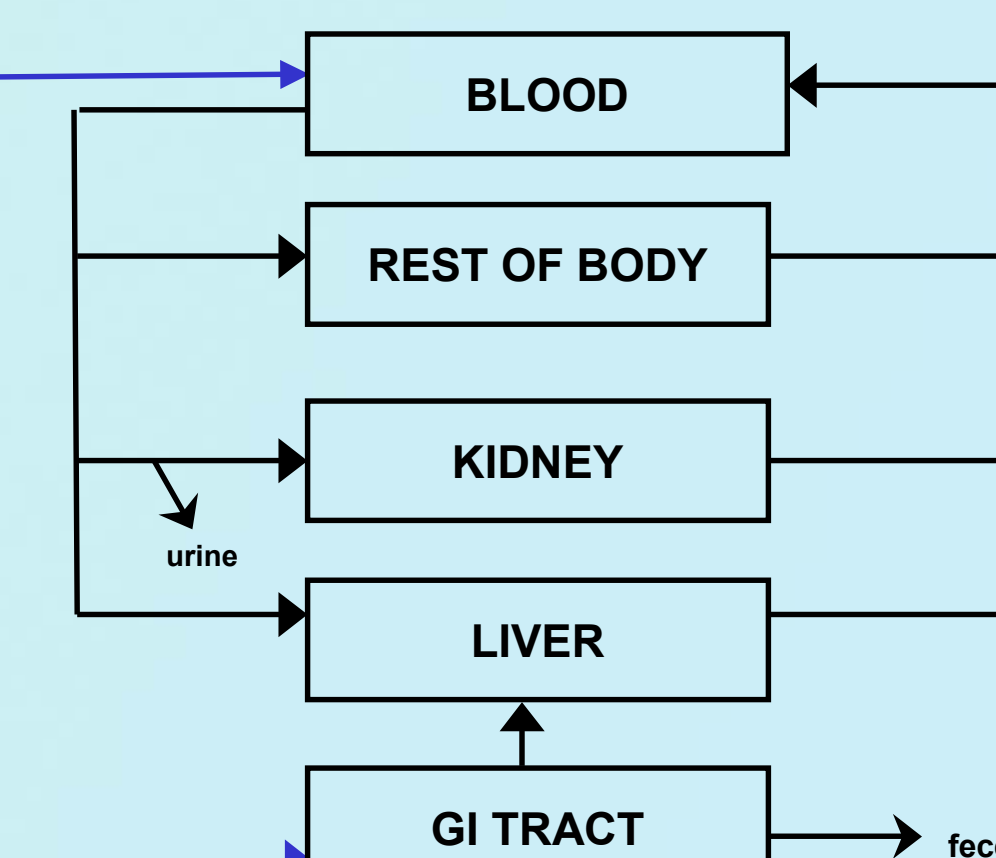
1. growing compartments for the fat, the uterus, the mammary tissue, and the placenta to simulate pregnancy.
2. a sub-model for the fetus/growing pup.

Pregnant/Lactating Female



Note: At birth, equations for the uterus, and the placenta will be turned off and equations representing lactational transfer will be turned on (see yellow boxes and blue arrows).

Fetus/Growing Pup



III. Results

- ❖ A review of the existing experimental data has been initiated.
- ❖ An initial formulation of the model structure (above) is being explored.

IV. Conclusions and Impact

This model can play a significant role in a developmental risk assessment of PFOS by providing a framework for dose-response analyses to be performed across the different life stages.

V. Future Directions

- The adult model (A) will be implemented and parameterized using AcslXtreme™ (Aegis Technologies Group, Inc., Huntsville, AL) .
- Additional complexity in the model structure may be added if necessary (e.g., additional tissues or more complex descriptions of existing tissues).
- The adult model will be extended to (B) to simulate PFOS kinetics in pregnant, lactating, fetal, and neonatal rats and mice.
- Longer term goals include extending the model to simulate exposure to other perfluorinated chemicals.

References

- Giesy JP and Kannan K (2001). Distribution of perfluorooctane sulfonate in wildlife. *Environ Sci Technol*. 35(7): 1339-42.
- Olsen GW et al. (1999). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. *J Occup Environ Med*. 41(9): 799-806.
- Olsen GW et al. (2003) Human donor liver and serum concentrations of perfluorooctanesulfonate and other perfluorochemicals. *Environ Sci Technol*. 37(5): 888-91.
- Renner R (2001). Growing concern over perfluorinated chemicals. *Environ Sci Technol*. 35(7): 154A-160A.
- 3M (1999). Combined Oral (Gavage) Final Report: Fertility, Developmental, Perinatal/Postnatal Reproduction Toxicity Study of PFOS in Rats. 3M. St. Paul, MN. June 10, 1999.

